132

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PUBLIC HEALTH SERVICE

National Institute of Mental Health
Addiction Research Center
U.S. Public Health Service Hospital
Lexington, Kentucky

26 May 1958

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The National Institute of Mental Health (Mr. Gordon Klovdahl) has informed me that he has asked the NIH budget office to forward the request for renewal of the synthetic substitutes for codeine project to the Office of Naval Research. The amounts requested will be identical with those given in the budget that I left with you.

The Institute has requested an increase in their appropriation in the hope of being able to take over some of the personnel assigned to this project, but this matter cannot be settled until the budget for fiscal 1959 is known exactly. In case they do take over any of the personnel then arrangements will be made to return whatever part of the funds that will not be required. Please let me know if this meets with your approval.

I am enclosing a print of the slide that I used in a Seminar at Bethesda. Although of not great interest, it does show the comparative psychotomimetic potencies of all the compounds I have tested for the Sandoz Company.

I currently have been working with the Japanese compounds from the Takeda Company (agroclavine and dihydroagroclavine). Neither compound has shown any psychotomimetic potency in doses ranging up to 50 mcg./kg. of body weight. On the contrary, agroclavine may have sedative properties. Another compound

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B-3

obtained from Eli Lilly and Company, in which the acid amide group of LSD has been replaced with the methyl and a hydroxyl, has also sedative rather than psychotomimetic properties. I am going to try agroclavine and the Lilly compound as possible blockers of LSD.

I will be leaving June 5th for an extended trip to the West coast and will not return to Lexington until the middle of July.

With kindest personal regards,

Sincerely yours,

Harris Isbell, M.D.
Director

HI:lw

Enclosures

B-38

Design. A randomized, double-blind design was used in both experiments. In both, two drug combinations were used: BOL plus LSD, and BOL placebo plus LSD. The combinations of BOL placebo plus LSD placebo and of BOL plus LSD placebo were not done because previous data indicate there was no change of significant degree after either combination.

Measurements. Systolic blood pressure, pupillary size and threshold for kneejerks were determined twice before and at hourly intervals for eight hours after LSD by methods previously described. A modification of the Jarvik-Abramson questionnaire was given twice before and 1/2, 1-1/2, 2-1/2, 3-1/2, 4-1/2, 5-1/2, 6-1/2 and 7-1/2 hours after LSD. Short mental status examinations were conducted at these times, in order to assign a "clinical grade" to the reaction.

Analysis of Data. Areas representing change from predrug controls were calculated for data on blood pressure, patellar reflex and pupillary size. The number of questions scored positively after LSD were counted, eliminating any which were also scored positively before LSD. Grades were assigned according to the system previously described. The usual statistical treatments were performed on the data. The t-test for paired observations and non-parametric tests (Wilcoxon) were used in evaluating the significance of results.

RESULTS

Experiment 56-D. The results of this experiment are shown in tables 56-D1 and 56-D2. All aspects of the LSD reaction were reduced but not to a statistically significant degree. This result is similar to that observed in our first experiment in which a larger dose of LSD was used.

Experiment 56-E. The results are shown in tables 56-E1 through 56-E3. Significant reductions (t-test) were observed in every aspect of the LSD reaction except for the patellar reflex. The non-parametric tests were also significant for every aspect except the clinical grade. Time course of the LSD reaction (table 56-E3) was not greatly altered by BOL, despite the evident attenuation.

DISCUSSION

The results show that pretreatment with BOL for five days does reduce the intensity of the reaction induced by 1 mcgm./kg. of LSD. The results strongly suggest that the longer BOL is administered the greater is the reduction in intensity of the reaction. Such results are more compatible with the development of some degree of cross tolerance between BOL and LSD than with direct competition of these drugs for receptor sites. The degree of cross tolerance to LSD conferred by pretreatment with BOL is, however, not complete. Even after

five days pretreatment with BOL significant changes over control occurred in blood pressure, pupillary size, and mental responses. There was also a marked variation between individuals. In several patients cross tolerance appeared to be almost complete; in others, only partial tolerance was observed.

CONCLUSION

Pretreatment with 1 mg. of BOL three times daily for five days causes a significant reduction in intensity of the reaction induced by 1 mcgm./kg. of LSD.

TABLE 56-D1.

Attempted Blocking of Reaction Induced by 1 mcgm. of LSD By Administration of 1 mg. of BOL t.i.d. for Two Days.

MEASURE	BOL AND LSD	BOL PLACEBO AND LSD
Patellar Reflex	5.2 ± 1.38	5.6 ± 1.78
Pupillary Size	14.6 ± 1.56	18.5 ± 2.12
Systolic Blood Pressure	77.4 ± 16.7	109.3 ± 12.2
Questions	53 ± 17.6	93 ± 24.9
Grade	2.0 ± 0.4	2.9 ± 0.3

TABLE 56-D2.

Number of Patients in Which Change
After BOL Placebo Was Greater Than After BOL.

MEASURE	CHANGE GREATER	CHANGE SMALLER	NO CHANGE
Kneejerk	5	3	0
Pupillary Size	5	3	0
Systolic Blood Pressure	6	2	0
Number of Questions	7	1	0
Grade	5	1	2

TABLE 56-E1.

Attempted Blocking of Reaction Induced by 1 mcgm./kg. of LSD By Five Days Pretreatment with 1 mg. of BOL t.i.d.

MEASURE	BOL AND LSD	BOL PLACEBO AND LSD
Patellar Reflex	5.08 ± 1.74	6.6 ± 1.33
Pupillary Size	9.55 ± 1.65	15.97 ± 1.78
Systolic Blood Pressure	50.3 ± 11.8	99.8 ± 17.1
Number of Questions	28 ± 14	66 ± 13
Clinical Grade	0.9 ± 0.45	2.0 ± 0.36

TABLE 56-E2.

Number of Patients in Which Change After BOL Placebo Was Greater than After BOL.

MEASURE	CHANGE GREATER	CHANGE SMALLER	NO CHANGE
Kneejerk	8	2	0
Pupillary Size	8	2	0
Systolic Blood Pressure	8	2	0
Number of Questions	8	2	0
Grade	6	1	3

TABLE 56-E3.

Time Course of LSD Reaction after Pretreatment with BOL or BOL Placebo for Five Days.

Treatment	C	1	2	3	4	5	6	7	8
					Pupillary Size				
					Hours after LSD				
BOL	4.2	5.7	5.8	5.8	5.6	5.4	5.3	5.2	5.2
BOL Placebo	4.2	6.1	6.8	6.8	6.6	6.5	6.1	6.1	5.9
					Systolic Blood Pressure				
BOL	106	111	111	111	114	112	112	114	115
BOL Placebo	104	116	117	118	119	119	118	114	116

					Number of Questions				
					Hours after LSD				
		1/2	1-1/2	2-1/2	3-1/2	4-1/2	5-1/2	6-1/2	7-1/2
BOL	0	2.7	5.4	6.3	4.9	3.4	2.7	2.1	0.7
BOL Placebo	0	7.9	16.9	17.0	12.2	6.7	3.3	1.0	0.5

Figures are averages of results on 10 patients.

BOL dosage was 1 mg. orally three times daily for five days prior to LSD plus 1 mg. two hours prior to LSD.

LSD dosage was 1 mcgm./kg.

C = Control (predrug) measurement.